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BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Paper No. 25

Application Number: 08/398,555

Filing Date: March 3, 1995

Appellant(s): Linda G. Cima et al

Collen A. Beard

For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed November 28, 1997.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 1-32. The petition for entry of the Amendment of September 4, 1997 was denied on December 15, 1997. Accordingly, this Answer does not address Appendix II or comments contained in the Answer directed to the proposed amended claims.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

The amendment after final rejection filed on September 4, 1997 has not been entered because, as noted above, the petition for entry was denied on December 15, 1997.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-32 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

5,032,508	Naughton et al	07-1991
5,171,264	Merrill	12-1992
5,370,681	Herweck et al	12-1994
5,512,474	Clapper et al	04-1996
5,522,895	Mikos	06/1996
EP 531,733	Sakai Enex	03-1993
WO 89/05616	Bio-Metric Systems	06-1989

Merrill, E. W. "Poly(ethylene oxide) star molecules: Synthesis, characterization, and applications in medicine and biology." J. Biomater. Sci. Polymer, Vol. 5, No. 1/2 (1993), pages 1-11.

Tomomura et al. "The Control of DNA Synthesis in Primary Cultures of Hepatocytes From Adult and Young Rats: Interactions of Extracellular Matrix Components, Epidermal Growth Factor, and the Cell Cycle." J. Cellular Physiology, Vol. 30 (1987), pages 221-227.

(10) New Prior Art

No new prior art has been applied in this examiner's answer.

(11) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "to enhance the rate of target cell growth" is indefinite because the term "enhance" is a relative term, but Applicants have not provided a basis with which to determine whether or not a particular rate of target cell growth is enhanced or not and thereby embraced within the scope of the claims. There are multiple possible bases for comparing growth rates, e.g., they can be compared to a composition which does not contain growth effector molecules, to a composition which contains growth effector molecules which are not tethered to a substrate, or to a composition containing tethered growth effector

molecules at a relatively low concentration. In the absence of a specific basis, it is not possible to determine whether or not a growth rate is enhanced or not. At claim 5, line 1, the phrase "the polymer" is indefinite because it is not clear if this refers to the "biocompatible synthetic polymeric tethers" or to the biocompatible polymers which form the biocompatible substrate. For analogous reasons, the phrase "the polymer" at claim 6, line 1; claim 21, line 1; and claim 22, line 1; is indefinite.

Claim 8 is rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. Independent claim 1 has been limited to require a synthetic polymeric tether. However, dependent claim 8 recites that the tether can be starch, which is a naturally-occurring material. Accordingly, dependent claim 8 does not further limit independent claim 1 but rather to some extent broadens it.

Claims 1-9, 13, 18-25, and 31 are rejected under 35 U.S.C. § 102(b) as being anticipated by Clapper et al. Clapper et al. disclose a cell culture support consisting of a support material, a positively-charged molecule and a cell adhesion factor (see claim 7). It is disclosed that "the positively-charged molecule and the cell adhesion factor are covalently bound to one another and either the positively-charged molecule or the cell adhesion factor is covalently bound to the supporting surface" (see claim 7 (b)). Clapper et al. disclose that the support material can be prepared from many materials including synthetic polymers (see column 5, line 36 - 50), zirconia, alumina, glass and silica (see column 5, lines 52 - 53). It is

disclosed that this cell culture support can be "in any suitable form, for instance, as membranes, tubes, microtiter wells, columns, hollow fibers, roller bottles, plates, dishes, and solid, hollow, or porous beads" (see column 5, lines 55 - 58). It is disclosed that the positively-charged molecule are synthetic (see column 7, line 44) and include carboxy methyl cellulose (see column 7, line 67). Clapper et al. disclose that the cell adhesion molecule include the extracellular matrix molecules "laminin, fibronectin, collagens (all types), vitronectin, and tenascin" (see column 6, lines 40 - 41). Clapper et al. disclose that this cell culture support can be used for "cell culture of mammalian cells" (see column 1, line 21). The cell adhesion molecules are present in amounts sufficient "to attract anchorage-dependent cells to the surface of the cell culture system, in order to allow the growth and/or spreading of such cells once attracted" (column 4, lines 63-67) and "to increase the rate at which such cells grow and spread on that surface" (column 6, lines 33-34). Because the cell adhesion molecules are ultimately covalently bound to the supporting surface, inherently they will not be able to be internalized by the cells.

Claims 10 - 12 and 26 - 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Clapper et al. Application of Clapper et al is the same as in the above rejection of claims 1-9, 13, 18-25, and 31. Clapper et al. disclose polymers as the positively charged molecules, but do not disclose backbone length of the polymers. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal backbone lengths for the positively charged molecules of

Clapper et al. because degree of polymerization, i.e. backbone length, is an art-recognized, result-effective variable which is routinely determined and optimized in any art involving polymers.

Claims 1 - 9, 13 - 16, 18 - 25 and 31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264). Herweck et al. disclose a device which can be used for stimulating the growth of eukaryotic blood cells (see Abstract and column 11, lines 24 - 49) and using this device as a "matrix and support upon which cellular matter is grown" (column 11, lines 26 - 27). This device consists of a substrate which can be manufactured from any suitable biocompatible material including fibers and polymers (see column 8, lines 44 - 57). Herweck et al. disclose that the substrate of the device can be shaped in any way needed for its required application (see column 4, lines 21 - 25). This device is also disclosed to be implantable (Abstract, line 1) and useful for treating a patient in need of cell growth (column 4, lines 39 - 40 and claim 28). Herweck et al. also disclose coating the substrate of the device with bioactive material such as platelet derived growth factor, epidermal growth factor, transforming growth factor, erythropoietin, and fibroblast growth factor (see claim 25 and column 12, lines 1 - 35). Herweck et al achieve an enhanced rate of target cell growth, i.e. growth of cells at the implantation site is enhanced compared to if no implantation had been made, and certain factors which can be present stimulate, i.e. enhance, endothelial cell growth (column 6, lines 23-29 and 33-36). Herweck et al. do not disclose biocompatible tethers which have one end covalently linked to the

substrate and a growth effector molecule covalently linked to the other end. Merrill discloses star molecules composed of biocompatible, non-thrombogenic, water-soluble polyethylene oxide (PEO)(see Abstract and column 1, line 21) which can have one arm covalently linked to a substrate thereby anchoring the molecule (see column 2, lines 11 - 14) and another arm covalently linked to a bioactive molecule (see column 5, lines 3 - 8 and claim 15). It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to make a composition for use in stimulating the growth of eukaryotic blood cells consisting of a biocompatible substrate, biocompatible tethers and growth effector molecules as described by Herweck et al. using the polyethylene oxide star molecules for the biocompatible tether components as described by Merrill because the star molecules will prevent thrombogenesis from occurring when the device of Herweck et al. is implanted while still ensuring that the device remains coated with the bioactive material.

Claims 10-12 and 26-28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264) as applied against claims 1-9, 13-16, 18-25, and 31 above and further in view of Merrill (J. Biomater. Sci. Polymer). Merrill discloses that the "length of each PEO chain corresponds to its molecular weight and typically range from about 1,000 to about 10,000" (see column 2, lines 56 - 58). Merrill (J. Biomater. Sci. Polymer) discloses that the arms of PEO consist of varying numbers of ethylene oxide monomers (CH_2OCH_2) (see page 3). The molecular weight of one of these monomers is 44 daltons. Therefore, a PEO chain of 1,000 daltons would correspond to approximately 23

monomers corresponding to approximately 68 backbone atoms and a PEO chain of 10,000 daltons would correspond to approximately 680 backbone atoms. Therefore, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to design a composition for stimulating the growth of eukaryotic cells as described above and choosing a PEO chain length such that the backbone of the tether (i.e. from substrate to growth effector molecule would include 2 PEO chains and the central divinyl benzene molecule which is 8 atoms) could vary in length between about 136 and 1360 atoms as suggested by Merrill (J. Biomater. Sci. Polymer); optimization within this range would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made because Merrill '764 discloses chain length to be a result-effective variable.

Claim 17 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264) as applied against claims 1 - 9, 13 - 16, 18 - 25 and 31 above, further in view of Mikos. Neither Herweck et al. nor Merrill disclose a substrate which is biodegradable. Mikos discloses a "biodegradable, bioresorbable , three-dimensional template for repair and replacement of diseased or injured bone which provides mechanical strength to bone while also providing a guide for growth of bone tissue" (see Abstract, lines 1 - 4). Mikos discloses that "the implant is seeded with osteoblasts prior to implantation to provide regeneration sites for bone tissue" (see column 1, lines 64 - 63). It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to make a cell growth composition outlined in the above rejection using a

biodegradable material as described by Mikos because a patient in need of an implantable cell growth composition might only need it for a defined period of time and it would be less deleterious to the patient and more conducive to overall healing to have the cell growth composition biodegrade and be bioabsorbed so that further surgery and trauma to the patient would not be necessary.

Claims 29 and 32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264) as applied against claims 1 - 9, 13 - 16, 18 - 25 and 31 above, further in view of Naughton et al. Neither Herweck et al. nor Merrill disclose using a cell growth composition for parenchymal or stem cells. Additionally, neither Herweck et al. nor Merrill disclose using a cell growth composition for testing a compound for its effect on tissue. Naughton et al. disclose a "three-dimensional cell culture system which can be used to culture a variety of different cell" (see Abstract, lines 1 - 3). It is disclosed that this system can be used to culture parenchymal cells and stem cells (see column 13, last paragraph continuing to column 14). Naughton et al. also disclose using this system in cytotoxicity assays (see column 1, line 33 - 34). It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the cell growth composition outlined in the above rejection to culture parenchymal and stem cells and to perform cytotoxicity assays, both as described by Naughton et al., because different cell culture methods are routinely sought in the cell culture art and because *in vitro* drug testing

methods are preferable to *in vivo* drug testing methods so that animals are not harmed and cost is contained.

Claims 29 and 30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264) as applied against claims 1 - 9, 13 - 16, 18 - 25 and 31 above, further in view of Tomomura et al. Neither Herweck et al. nor Merrill disclose using a cell growth composition for hepatocytes. Tomomura et al. disclose that "rat hepatocytes in primary cultures lack the ability to proliferate" (Introduction, paragraph 1, lines 5 - 6) and that cultured rat hepatocytes are stimulated to replicate by addition of epidermal growth factor (see Abstract). It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the cell growth composition outlined in the above rejection with epidermal growth factor as the growth effector molecule for cell culture of hepatocytes because such a cell culture would be useful because the liver is the "detoxification center" of the body, however, when acting upon a compound, the liver may convert it to a form which is also toxic or in some way deleterious to the organism, so it would be useful to have long term cultures of hepatocytes to use for *in vitro* biotransformation reactions of chemicals, the biotransformation products of which could then be tested *in vitro* on other cultured cell types.

Claims 1-7, 9, 10, 13, 18-21, 23, 25, 26, 29, 30, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by the European Patent Application '733. The European Patent Application '733 teaches a carrier, e.g., a cellulose foam in the form of a cube, a rectangular

parallelpiped, a globular shape, or chopped into small pieces (page 4, line 29 - page 5, line 14) to which is covalently attached cell adhesive factors such as fibronectin, vitronectin, fibrinogen, laminin, collagen, gelatin and fetuin (page 2, lines 56-57), i.e. extracellular matrix proteins, and cell growth factors such as EGF, PDGF, FGF, and IF (page 3, lines 22-25) through a spacer made from a biocompatible synthetic polymer such as a polyethyleneimine or a polyamino acid (page 3, line 42 - page 4, line 25), i.e. a tether. Animal cells such as hepatocytes are cultured on the carriers (page 5, lines 18-28). The invention permits cells to be cultured in a higher density and larger quantity in comparison with conventional carriers (page 5, lines 29-31). Because the cell adhesive factors and cell growth factors are covalently attached to the carrier of the European Patent Application '733, inherently they will not be able to be internalized by the cells. Because the structure and chemical composition of carriers of the European Patent Application '733 are the same as is recited in Applicants' claims, and because of the higher cell density achieved by the European Patent Application '733, inherently the rate of target cell growth will be enhanced in the European Patent Application '733 to the same extent claimed by Applicants.

Claims 10-12 and 26-28 are rejected under 35 U.S.C. 103(a) as being obvious over the European Patent Application '733. Application of the European Patent Application '733 is the same as in the above rejection of claims 1-7, 9, 10, 13, 18-21, 23, 25, 26, 29, 30, and 31. The European Patent Application '733 discloses spacer size to be an art-recognized result-effective variable (page 3, lines 51-53, and page 4, lines 21-23) but does not describe the size

in terms of the number of backbone atoms. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal backbone lengths for the spacers of the European Patent Application '733 because spacer size is an art-recognized, result-effective variable as disclosed by the European Patent Application '733 and because determining spacer size will also result in determining the backbone length of the spacer.

Claims 1-10, 12-26, 28, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application '616. The WO Patent Application '616 teaches a support surface, e.g., a biocompatible polymer such as polyurethane, polyester, skin, or cellulose in any desired shape including shapes suitable for implantation (page 7, line 28 - page 9, line 16) to which is covalently attached biomolecules such as ECGF, FGF, PDGF, and collagen (page 7, lines 14-27) through a spacer preferably made from a polyethylene oxide at least 25 angstroms long, e.g. having a size of 1450 daltons which is equivalent to a backbone length of about 99 atoms (page 7, lines 2-8, and pages 20-24), i.e. a tether. Animal cells such as endothelial cells are cultured on the carriers (pages 20-24). The invention permits the loading density of biomolecules to a support surface to be increased (page 14, lines 27-30). Because the biomolecules are covalently attached to the support surface of the WO Patent Application '616, inherently they will not be able to be internalized by the cells. Because the structure and chemical composition of carriers of the WO Patent Application '616 are the same as is recited in Applicants' claims, and because of the higher biomolecule loading density

achieved by the WO Patent Application '616, inherently the rate of target cell growth will be enhanced in the WO Patent Application '616 to the same extent claimed by Applicants.

Claims 11 and 27 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application '616. Application of the WO Patent Application '616 is the same as in the above rejection of claims 1-10, 12-26, 28, and 31. The WO Patent Application '616 discloses spacer size to be an art-recognized result-effective variable (page 7, lines 2-5) but does not teach a spacer size of between 100 and 50,000 atoms. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal backbone lengths for the spacers of the WO Patent Application '616 because spacer size is an art-recognized, result-effective variable as disclosed by the WO Patent Application '616 and because determining spacer size will also result in determining the backbone length of the spacer.

(12) New Ground of Rejection

This examiner's answer does not contain any new ground of rejection.

(13) Response to argument

Appellants contend: (1) that the meaning of the term "enhance" is readily understood when read in light of the specification; (2) that the term "polymer" in claims 5, 6, 21, and 22 clearly refers to the biocompatible polymer recited in claims 4 and 20 upon which they depend; (3) that Clapper et al teach cell adhesion factors rather than growth effector molecules as claimed by Appellants; (4) that Clapper et al do not teach that the tethered cell adhesion

factors increase the rate of cell growth; (5) that Clapper et al's use of a positively charged tether molecule teaches away from Appellants' claimed invention; (6) that the European Patent Application '733 teaches a growth effector molecule which is immobilized on a substrate rather than tethered as is required by Appellants' claims; (7) that the polyethyleneimine spacer of the European Patent Application '733 is positively charged and will attract and interact with proteins and cells, whereas Appellants' polymers do not interact with cells but will provide a wide range of movement (flexibility) to the factors attached thereto; (8) that the European Patent Application '733 does not disclose that its compositions enhance the rate of cell growth over the rate of cell growth due to soluble or adsorbed growth effector molecule; (9) that the only examples in the WO Patent Application '616 involving cells demonstrate tethering of collagen, hyaluronic acid, and fibronectin; (10) that the WO Patent Application '616 does not report enhanced cell growth and does not include comparisons of tethered growth effector molecules versus soluble or adsorbed growth effector molecules; (11) that the WO Patent Application '616 does not teach how to tether EGF to alter cell growth; (12) that it would not be obvious to optimize tether length in Clapper et al because Clapper et al do not disclose Appellants' goal of a flexible tether which does not bind to the cells of interest; (13) that there is no suggestion in either Herweck et al or in Merrill '264 to incorporate the teachings of the other reference, that Herweck et al do not suggest that it would be advantageous to tether the factors to the substrate, that Merrill '264 does not suggest using the star molecules for tethering growth effector molecules to a substrate, and that the primary use of Merrill '264's

star molecules is for separating and purifying therapeutic proteins; (14) that Herweck et al and Merrill '264, even if combined, do not disclose how to enhance cell growth; (15) that use of antithrombogenic polymers such as the polyethylene oxide of Merrill '253 would have been expected to repel cells and would therefore have been expected to prevent contact between the cells and the bioactive materials of Herweck et al; and (16) that one of ordinary skill in the art would be led by the disclosure of Naughton to believe that no further modifications were necessary in order to grow cells.

With respect to contention (1), the word "enhance" implies a comparison, but the claims are not clear as to what comparison is to be made. The rejection notes several possible bases for comparing target cell growth rates, and the Brief recites two, i.e. that target cell growth rates should be compared to soluble molecules or to absorbed molecules. However, with respect to Appellants' citations to their specification, it should be noted that page 5, lines 6-30, and page 15, line 27 - page 16, line 2, which are a more general description of the invention, discuss the enhancement of target cell growth rates only with respect to soluble molecules; page 24, lines 16-22, which is a specific example, discusses the enhancement of target cell growth rates only with respect to adsorbed molecules. These citations do not establish that soluble molecules and adsorbed molecules were intended to be alternatives to one another in determining whether or not an enhanced rate of target cell growth has been achieved. Further, it is not proper to read into a claim a limitation found only in an example, because an example is not a definition. Where multiple different meanings can be attributed to

the same claim terminology, and where the specification does not clearly set forth which meaning was intended by Applicants, the claim terminology is indefinite.

With respect to contention (2), while it is agreed that claims 5, 6, 21, and 22 depend upon claims 4 or 20, they also depend upon claims 1 and 13. The language of claims 5, 6, 21, and 22, i.e. "the polymer" is not identical to the language either of claims 4 and 20 ("biocompatible polymers") or of claims 1 and 13 ("biocompatible synthetic polymeric tethers"). Accordingly, it is not clear to which polymers the phrase "the polymer" refers.

With respect to contention (3), the laminin, fibronectin, collagen, vitronectin, and tenascin taught by Clapper et al are extracellular matrix molecules, which are specifically claimed by Appellants as growth effector molecules (see claims 9 and 25). Further, these factors are specifically described as increasing the rate at which cells grow and spread on a surface (see column 6, lines 31-34) and for this reason also they constitute growth effector molecules.

With respect to contention (4), Clapper et al do teach that the invention "improves the attachment and growth of 'anchorage dependent cells'" (column 5, lines 65-66), that the cell adhesion factor increases the rate at which such cells grow and spread on the surface (column 6, lines 31-34), that the density of the cell adhesion factor should be sufficient "to promote cell attachment and growth" (column 7, lines 14-16), that the invention results in better growth of cells (column 10, lines 29-34), and that covalently attached cell adhesion proteins are more effective than adsorbed cell adhesion proteins (column 10, lines 61-65). This disclosure

anticipates Appellants' claim requirement that the tethered growth effector molecules result in enhanced rate of target cell growth. Further, the components and structure of the compositions of Clapper et al are the same as is recited in Appellants' claims, namely a cell adhesion factor, i.e. a growth effector molecule, is covalently linked to a positively charged polymer, i.e. a tether, which is covalently linked to the surface of a cell culture support, i.e. a biocompatible solid substrate. Because Clapper et al's and Appellants' compositions are the same and are used in the same methods, necessarily the compositions must have the same properties and methods of using the compositions must yield the same results.

With respect to contention (5), Appellants' claims do not contain any language which would exclude from their scope the positively charged tether molecules of Clapper et al. Patentability cannot be based upon unclaimed differences over the prior art. Appellants' claims also do not require their tethers to be flexible and do not require them not to interact with the cells, as implied at page 16, line 18, of the Brief. Clapper et al's tethers do not apparently "discourage" interaction of the growth effector molecules with the cell receptors, at least not in any practical sense, because Clapper et al's invention, like Appellants' claimed invention, results in the growth of cells in culture.

With respect to contention (6), the European Patent Application '733 does not teach an adsorbed cell growth factor composition; rather, it teaches cell growth factors covalently attached (see, e.g., page 3, lines 8-9; page 4, lines 24-25; and page 6, lines 10-16) through a spacer to a substrate. There is no difference between a growth effector molecule which is

immobilized on a substrate through a spacer, as is taught by the European Patent Application '733, and a growth effector molecule which is tethered to a substrate as is claimed by Appellants. In fact, Appellants' specification uses the terms "immobilization" and "tethering" interchangeably, e.g., in the Detailed Description of the Invention at page 5, lines 6-16; Appellants' specification teaches that "spacer molecules... are expected to be suitable for forming tethers" (page 8, lines 22-23); and Appellants' specification teaches the use of the same class of attachment agents (see page 12, line 17 and 19) as are used by the European Patent Application '733 (see page 6, lines 11 and 15). Neither Figure 2 nor page 24 of the specification, cited in Appellants' Brief, discloses a difference between immobilization and tethering.

With respect to contention (7), none of Appellants' claims exclude polymers which have a positive charge or polymers which will interact with cells or proteins. None of Appellants' claims require the polymers to be flexible. Patentability must be based upon claimed, not unclaimed, differences over the prior art. In any event, the spacers of the European Patent Application '733 are flexible. Please note the discussion at page 3, lines 42-44 and 53-55, which discloses that the use of spacers permits the growth factors to "freely change position within a given space without being fixed to a particular position."

With respect to contention (8), the European Patent Application '733 covalently links the same growth effector molecules through the same spacers to the same substrates as are claimed by Appellants. Because the growth effector molecules of the European Patent

Application '733 are "tethered" rather than soluble or adsorbed, they will increase the rate of cell growth to the same extent claimed by Appellants. The European Patent Application '733's disclosed objects, i.e. to "promote cell growth" (page 2, line 42) and to enable "a desired product to be produced with higher efficiency" (page 2, lines 44-45) are fully consistent with Appellants' intended result. Neither the claims nor the specification require a specific concentration of growth factors on a substrate; in fact, Appellants' specification describes the concentration merely as being the result of immobilization of the growth effector molecules to the substrate (see page 5, lines 13-15). Because the growth effector molecules of the European Patent Application '733 are immobilized, or tethered, to the same extent as Appellants' growth effector molecules, the growth effector molecules of the European Patent Application '733 will be present in a sufficient concentration to the same extent as Appellants' growth effector molecules.

With respect to contention (9), the disclosure of the WO Patent Application '616 is not limited to the reference's examples. The WO Patent Application '616's specific teaching of ECGF, FGF, and PDGF (see page 7, lines 16-20) is not dependent upon whether or not there is an example using these growth factors. Further, collagen, hyaluronic acid, and fibronectin, which as pointed out by Appellants are specifically exemplified by the WO Patent Application '616, are extracellular matrix molecules, i.e. are a type of growth effector molecule specifically claimed by Appellants (see claims 9 and 25). Accordingly, the WO Patent Application '616 is not distinguished even by limiting its disclosure to the working examples.

With respect to contention (10), the WO Patent Application '616 reports a composition containing the same components in the same structural relationship as the composition claimed by Appellants. Whether recognized by the prior art or not, inherently the composition of the WO Patent Application '616 will enhance growth of cells to the same extent claimed by Appellants because the compositions are the same and are used for the same purpose. It is not relevant to a prima facie case of anticipation that the motivations of the prior art are different than Appellants, that the prior art disclosure uses different terminology than Appellants, or that the prior art doesn't teach the same comparative examples disclosed by Appellants. The issue is whether or not the compositions and methods are the same, and Appellants point to no differences between the compositions and methods of the WO Patent Application '616 and the compositions and methods of Appellants' claimed invention.

With respect to contention (11), none of Appellants' claims require the presence of EGF. Accordingly, the WO Patent Application '616 need not teach EGF in order to anticipate Appellants' claims.

With respect to contention (12), again Appellants' claims do not require a flexible tether which does not bind to the cells of interest, and therefore Clapper et al's lack of this goal does not negate motivation, reasonable likelihood of success, or obviousness. For any polymer, one of ordinary skill in the art routinely considers and optimizes the degree of polymerization, i.e. size or length. There is no indication in Clapper et al that the size of the

polymer affects whether or not cells will grow in the inventive culture, and Appellants have not submitted any evidence of criticality for tether size.

With respect to contention (13), obviousness based upon the combination of Herweck et al with Merrill '264 does not require Herweck et al or Merrill '264 expressly state their combination with the other patent. Further, while the examiner agrees that Herweck et al does not suggest that it would be advantageous to tether the factors to the substrate, and that Merrill '264 does not suggest using the star molecules for tethering growth effector molecules to a substrate, it is only to be expected in an obviousness rejection combining references that each of the references does not teach or suggest some aspect of the claimed invention. The disclosure of Merrill '264 is not limited to Merrill '264's disclosed "primary use"; rather, the disclosure of Merrill '264 as a whole must be considered, in combination with the other prior art of record, in determining the obviousness of the claims. Merrill '264 discloses polyethylene oxide star molecules which can be simultaneously covalently linked to a substrate and to a bioactive molecule and which can be used to coat biomedical devices to be used in vivo to prevent thrombosis as the locations of the device. Herweck et al disclose biomedical devices to be used in vivo. Because it is desirable in the art to prevent thrombosis, it would be desirable to coat the biomedical device of Herweck et al with the polyethylene oxide of Herweck et al.

With respect to contention (14), Herweck et al teach an enhanced rate of growth, i.e. growth of cells at the implantation site is enhanced compared to if no implantation had been

made. (Note that as indicated in the above rejection under 35 U.S.C. 112, second paragraph, the term "enhance" is susceptible to multiple interpretations, and therefore this interpretation is as valid as the ones proposed by Appellants.) Tethering of the bioactive materials of Herweck et al through the polyethylene oxide of Merrill '264 would still result in the bioactive materials being present at the implantation site, and therefore an enhanced rate of growth would have been expected to be maintained.

With respect to contention (15), Merrill '264 at column 1, lines 6-9, states that polyethylene oxide "does not absorb proteins of the intrinsic clotting system nor of the platelet membrane". This does not mean, as concluded by Appellants, that POE repels cells, because repulsion is not the negation of absorption and the POE may merely be inert with respect to cells. It also does not follow, merely because polyethylene oxide does not absorb proteins of the intrinsic clotting system nor of the platelet membrane, that all cells would necessarily be repelled. Platelets are only one type of the many different cells found in vivo, and in particular are not the type of cells whose growth Herweck et al intend to promote with their implant (see, e.g., column 11, lines 24-49). Even assuming that the POE of Merrill '264 did repel platelets, this is preferable in its combination with Herweck et al which desires blood circulation through the implant and not clotting (column 11, lines 24-27).

With respect to contention (16), a reference never teaches away from modification on the basis that the reference's disclosure is "adequate"; otherwise, for example, a U.S. patent

could never form the basis of a rejection under 35 U.S.C. 103 because by presumption all U.S. patents are "adequate" for their disclosed purposes.

With respect to the rejections under 35 U.S.C. 103(a) based upon the European Patent Application '733 or upon the WO Patent Application '616, Appellants apparently argue that the rejections stand or fall with the anticipation rejections based upon the same references (see the Brief at page 24, last two paragraphs). With respect to the rejections under 35 U.S.C. 103(a) based upon Herweck et al in view of Merrill '264 and further in view of Merrill (J. Biomater. Sci. Polymer) or Mikos or Tomomura, Appellants apparently argue that the rejections stand or fall with the obviousness rejection based upon Herweck et al in view of Merrill '264 (see the Brief at page 27, second paragraph through page 28, line 2, and page 28, last paragraph). The examiner agrees with this argument.

Appellants did not argue or respond in the Brief to the rejection of claim 8 under 35 U.S.C. 112, fourth paragraph.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

JRUSSEL
PRIMARY PATENT EXAMINER
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